REMARKS

This amendment is in response to the Office Action, dated February 9, 2007, ("Office Action"). In the Office Action, Examiner indicated that claims 73, 74, 77, 78, 85 and 86 are allowed, for which Applicant thanks Examiner. Examiner further indicated that claims 6, 7, 25 and 64 were objected to but would be allowed if rewritten in independent form; and that claims 1, 4, 5, 8, 9, 11, 12, 15-23, 26, 28, 57-63, 65, 66, 71, 72, 75, 76, 79, 80, 87 and 88 were rejected. Claims 12, 60, 75, and 87 have been amended; and claims 26, 28, 32, 34, 65, 66, 69, 70, 79, 80, 83 and 84 have been canceled (claims 2-3, 13-14, 24, 27, 30, 33, and 35-56 having previously been canceled) by virtue of the present amendment. Claims 1-12, 15-23, 29, 57-64, 67-68, 71-78, 81-82 and 85-88 are pending after entry of the present amendment.

Claims 12, 60, 75 and 87 have been amended to recite that the hydroxy protecting groups are selected from the following: ether, ester, C1-C4 alkyl, substituted C1-C4 alkoxy, unsubstituted C1-C4 alkoxy, substituted C1-C6 alkyl, unsubstituted C1-C6 alkyl, SO_2-(C4-C6 alkyl), and (CO)Ar, wherein Ar is a benzyl or a substituted phenyl. No new matter has been added. Support for this amendment may be found in the specification on pages 7-8.

In the Office Action, Examiner stated that the earliest effective U.S. filing date afforded to the claims was July 23, 2003 (the filing date of the instant application) because provisional application serial No. 60/290,307, filed on May 10, 2001, and the non-provisional application serial No. 10/142,087, filed on May 9, 2002, did not provide support for the following: (1) claims reciting a dose range of 180-300 mg per day; (2) the administration of an estrogen lowering drug; and (3) the prodrug formulas in claims 12, 60, 75 and 87.

Examiner rejected claims 12, 15-22, 26, 28, 60-62, 65-66, 72, 75-76, 79-80 and 87-88 under 35 U.S.C. §112, first paragraph as failing to comply with the written description requirement. Examiner stated that the specification disclosed prodrugs

having formula IV and specific hydroxyl protecting groups recited on page 8 of the specification. However, Examiner found that the claims encompassed a broad class of structurally diverse hydroxyl protecting groups, which are not sufficiently described in the specification. Examiner also found that "the broad recitation of 'prodrug' has insufficient written description to support the genus encompassed by the claims." Examiner concluded that only prodrugs having formula IV and specific hydroxyl protecting groups, but not the full breadth of the claims would meet the written description requirement. With respect to canceled claims 26, 28, 65, 66, 79, and 80, this rejection is rendered moot. With respect to claims 12, 15-22, 60-62, 72, 75-76, and 87-88, Applicant respectfully traverses this rejection.

Applicant in no way concedes to the merit of the written description rejection. However, in the interest of expediting prosecution, Claims 12, 60, 75 and 87 have been amended to recite that the hydroxyl protecting groups are selected from the following: ether, ester, C1-C4 alkyl, substituted C1-C4 alkoxy, unsubstituted C1-C4 alkoxy, substituted C1-C6 alkyl, unsubstituted C1-C6 alkyl, SO_2-(C4-C6 alkyl), and (CO)Ar, wherein Ar is a benzyl or a substituted phenyl. Applicants respectfully submit that claims 12, 60, 75 and 87, as amended and claims 15-22, 61-62, 72, 76 and 88 that depend therefrom satisfy the written description requirement. As such, Applicant respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement.

Examiner rejected claims 1, 4-5, 8-9, 11, 23, 57-59, 63 and 71 under 35 U.S.C. §103(a) as being unpatentable over Kim *et al.* (Cancer Research, 2002, 62:5365-5369). Examiner found that Kim *et al.* disclosed that raloxifene induces apoptosis in androgen-independent human prostate cancer cell lines. Examiner further found that Kim *et al.* disclosed the following: (1) raloxifene was a selective estrogen receptor modulator (SERM) that binds to both estrogen receptor-α (ER-α) and estrogen receptor-β (ER-β); (2) raloxifene inhibited proliferation of the three prostate cancer cell lines in a dose dependent manner and induced apoptosis of two of the prostate cancer cell lines; (3) the raloxifene concentration used in the majority of the studies was 10^{-5} M and clinical trials have shown that serum concentration of raloxifene is in the 10^{-9} M range

when administered at a dose of 30-150 mg/day; (4) a suggestion that 10^{-6} M may not be achievable *in vivo*; and (5) the effect of raloxifene was observed initially in prostate cancer cell lines at 10^{-9} M after four days of treatment. Examiner found that the claims are obvious to one of ordinary skill in the art because the skilled artisan "would have been imbued with at least a reasonable expectation that raloxifene would be effective in treating prostate cancer given the disclosure of Kim *et al.*" Examiner further found that the claimed doses would have been readily determined through routine experimentation, which is further supported by the suggestion of Kim *et al.* that a dose of more than 150 mg/day may be needed. Applicant respectfully traverses this rejection.

As shown by the declaration of David B. Agus, M.D. (hereinafter "Agus Declaration") and the supporting exhibit, the date of conception of the invention as well as the date that the invention was reduced to practice occurred prior to the publication date of Kim *et al.* Thus, Kim *et al.* cannot provide the basis for the §103(a) rejection of claims 1, 4-5, 8-9, 11, 23, 57-59, 63 and 71.

As recognized by the Examiner, the present application claims benefit of priority to U.S. non-provisional patent application serial No. 10/412,087 filed May 9, 2002, which claims benefit of priority to U.S. provisional patent application serial No. 10/142,087 filed on May 10, 2001. The introduction of the dosage of about 180 mg to about 300 mg per day was part of the present application filed July 23, 2003. The publication date of Kim *et al.* was September 15, 2002.

However, the dosage of 180 mg was conceived and reduced to practice at least as early as June 17, 2002, as evidenced by the e-mail correspondence from Koo Nguyen, the Clinical Research Development Manager for the Prostate Cancer Center at Cedars-Sinai Medical Center, to the inventor, David Agus, to confirm that a patient will be taking raloxifene at 180 mg/day. (*See* Exhibit A and Agus Declaration ¶3.)

Based on the foregoing remarks, Applicant respectfully submits that the invention, as described in claims 1, 4-5, 8-9, 11, 23, 57-59, 63 and 71, was conceived and reduced to practice prior to the publication of Kim *et al.* As such, Kim *et al.* cannot be used as a prior art reference to form a rejection under §103(a). Applicant

respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a).

Examiner rejected claims 1, 4-5, 8-9, 11, 23, 57-59, 63 and 71 under 35 U.S.C. §103(a) as being unpatentable over Steiner *et al.* Examiner found that Steiner *et al.* disclosed the use of antiestrogens, including raloxifene, for the prevention and treatment of prostate cancer. The dosages disclosed by Steiner *et al.* were in the range of 5-80 mg/day. Examiner stated that one skilled in the art would appreciate that "prostate cancer" when used in Steiner *et al.* includes both androgen-dependent and androgen-independent prostate cancer. Examiner concluded that the skilled artisan would recognize that the methods disclosed in Steiner *et al.* could be used to treat androgen-independent prostate cancer. Examiner further stated that while Steiner *et al.* only defined a range of 5-80 mg/day, "optimization of doses effective to elicit a preferred pharmacological effect is routine in the art of chemotherapy." Examiner further asserted his position by stating that claim 5 recites that the administration of 180 mg/day is performed after a mammal fails to respond to 60 mg/day. Applicant respectfully traverses this rejection.

Applicant respectfully submits that claims 1, 4-5, 8-9, 11, 23, 57-59, 63 and 71 are not rendered obvious by Steiner *et al.*

First, Applicant respectfully disagrees with Examiner's statement that the skilled artisan would recognize that the methods disclosed in Steiner *et al.* could be used to treat androgen-independent prostate cancer. As described in the specification on page 2, lines 8-10, "[e]ven therapies that are highly effective at treating androgen-dependent cancers have been shown to be ineffective when applied to patients with androgen-independent cancer." While Steiner *et al.* discusses methods for treating prostate cancer, generally, Steiner *et al.* does not specifically teach that the administration of raloxifene will treat androgen-<u>independent</u> prostate cancer. Rather, Steiner *et al.* discusses methods for preventing prostate cancer by regressing prostate intraepithelial neoplasia and methods for treating prostate cancer. The models used in Steiner *et al.* for the prostate cancer were not androgen-<u>independent</u> models. Androgen-<u>independent</u> prostate cancer is difficult to treat and usually cannot be treated with therapies that are

effective at treating androgen-dependent prostate cancers (*see* specification, page 2, lines 6-11). Thus, one of skill in the art will not expect that the methods disclosed in Steiner *et al.* would successfully treat androgen-independent prostate cancer.

Second, even if one of ordinary skill in the art would expect that the methods disclosed in Steiner *et al.* would successfully treat androgen-independent prostate cancer, which Applicant in no way concedes, the invention as described in claims 1, 4-5, 8-9, 11, 23, 57-59, 63 and 71, is still not rendered obvious by Steiner *et al.* Examiner, in his August 22, 2006 Office Action had previously found that Steiner *et al.* "only define a limited range of doses (*i.e.*, 5-80 mg/day)" and only objected to a claim that recited a dosage that was outside of the limited range taught by Steiner *et al.* Further, as seen in the Examiner's Interview summary of October 12, 2006, Examiner agreed that dosages of about 180 mg to about 300 mg would overcome the prior art of record (*i.e.*, Steiner *et al.*).

Third, while Applicant notes Examiner's statement that "optimization of doses effective to elicit a preferred pharmacological effect is routine in the art of chemotherapy," Applicant respectfully submits that the dosages in claims 1, 4-5, 8-9, 11, 23, 57-59, 63 and 71, are not the product of routine optimization that can be based on Steiner *et al.* Steiner *et al.* taught doses of 5-80 mg/day. Steiner *et al.* continued on and taught ranges of "35-66 mg/day...40-60 mg/day...45-60 mg/day...15-25 mg/day...55-65 mg/day...45-60 mg/day...60 mg/day...20 mg/day... [and] 45 mg/day." (*See* Steiner *et al.* at column 6, lines 18-27.) One of skill in the art may consider these dosage ranges as optimization of a dosage as the dosages reflected different amounts that may be administered. However, the dosages instantly claimed (*e.g.*, 180-300 mg) are much higher and are not due to mere routine optimization. Moreover, one of basic criteria to establish a prima facie case of obviousness is that the "prior art reference...must teach or suggest all the claim limitations." (Emphasis added.) *See* MPEP §2142. It is apparent that Steiner *et al.* does not teach all the claim limitations. It is also apparent that based on the disclosure of Steiner *et al.*, it does not suggest all the claim limitations.

In light of the foregoing remarks, Applicant respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a).

Applicant respectfully submits that Claims 1, 4-9, 11, 12, 15-20, 22, 23, 25, 57-64, 71-78, and 85-88 are each allowable, of which claims 1, 12, 57, 60, 73, 75, 85, and 87 are generic and encompass species claimed by claims 10, 21, 29, 31, 67-68 and 81-82. Thus, claims 10, 21, 29, 31, 67-68 and 81-82 encompassing the species arzoxifene are also allowable.

All of the claims remaining in the application are now believed to be allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

If questions remain regarding this application, the Examiner is invited to contact the undersigned at (213) 633-6800.

Respectfully submitted,
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Attachments:
Declaration of David B. Agus, M.D.
Exhibit A.

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